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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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SUEDE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chemical compounds

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CHEMICAL COMPOUNDS

The present invention relates to quinazoline derivatives for use in the treatment of disease in particular proliferative diseases such as cancer and in the preparation of medicaments for use in the treatment of proliferative diseases, and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative diseases) are characterised by uncontrolled cellular proliferation. This loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, an ordered cascade of protein phosphorylation is thought to control the cell cycle. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle. For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase. The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6; 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. The three human homologues of these genes Aurora-A, Aurora-B and Aurora-C (also known as aurora2, aurora1 and aurora3 respectively) encode cell cycle regulated serine-threonine protein kinases (summarised in Adams *et al.*, 2001, Trends in Cell Biology. 11(2): 49-54). These show a peak of expression and kinase activity through G2 and mitosis. Several observations implicate the involvement of human aurora proteins in cancer. This evidence is particularly strong for Aurora-A. The Aurora-A gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora-A may be the major target gene of this amplicon, since Aurora-A DNA is amplified and mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours Aurora-A protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human Aurora-A leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of Aurora-A leads to an increase in centrosome number and an increase in aneuploidy, a known event in the development of cancer. Other work has shown an increase in expression of Aurora-B (Adams *et al.*, 2001, Chromsoma. 110(2):65-74) and Aurora-C (Kimura *et al.*, 1999, Journal of Biological Chemistry, 274(11): 7334-40) in tumour cells when compared to normal cells.

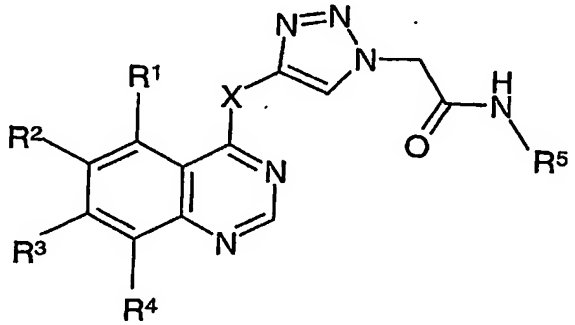
Importantly, it has also been demonstrated that abrogation of Aurora-A expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO 97/22702 and WO 99/37788) leads to cell cycle arrest and exerts an antiproliferative effect in these tumour cell lines. Additionally, small molecule inhibitors of Aurora-A and Aurora-B have been demonstrated to have an antiproliferative effect in human tumour cells (Keen *et al.* 2001, Poster #2455, American Association of Cancer research annual meeting). This indicates that inhibition of the function of Aurora-A and/or Aurora-B will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases. Further, inhibition of Aurora kinases as a therapeutic approach to these diseases may have significant advantages over targeting signalling pathways upstream of the cell cycle (e.g. those activated by growth factor receptor tyrosine kinases such as epidermal growth factor receptor

(EGFR) or other receptors). Since the cell cycle is ultimately downstream of all of these diverse signalling events, cell cycle directed therapies such as inhibition of Aurora kinases would be predicted to be active across all proliferating tumour cells, whilst approaches directed at specific signalling molecules (e.g. EGFR) would be predicted to be active only in the subset of tumour cells which express those receptors. It is also believed that significant "cross talk" exists between these signalling pathways meaning that inhibition of one component may be compensated for by another.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of Aurora kinases. For example, WO 01/21594, WO 01/21595 and WO 01/215968 describe the use of certain phenyl-quinazoline compounds as Aurora-A kinase inhibitors, which may be useful in the treatment of proliferative diseases and WO 01/21597 discloses other quinazoline derivatives as inhibitors of Aurora-A kinase. Additionally, WO 02/00649 discloses quinazoline derivative bearing a 5-membered heteroaromatic ring where the ring is, in particular, substituted thiazole or substituted thiophene. However despite the compounds of WO 02/00649 there still exists a need for further compounds having Aurora kinase inhibitory properties.

The applicants have been successful in finding a novel series of compounds which inhibit the effects of the Aurora kinases and in particular Aurora-A kinase and/or Aurora-B kinase which are thus of use in the treatment of proliferative diseases such as cancer, in particular in such diseases such as colorectal, breast or pancreatic cancer where Aurora kinases are known to be active. The compounds may also be useful in the treatment of leukaemia.

According to one aspect of the present invention there is provided a compound of formula (I)



formula (I)

or a salt, ester or prodrug thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{11}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by heterocyclyl, halo, hydroxy, C_{1-4}alkoxy or $-NR^9R^{10}$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{12}}$ is hydrogen, heterocyclyl or a group selected from aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by aryl, heterocyclyl, halo, hydroxy or $-NR^{15}R^{16}$;

$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{13}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by $-NR^7R^8$, heterocyclyl, halo, hydroxy or C_{1-4}alkoxy;

$\mathbf{R^7}$ and $\mathbf{R^8}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl;

or $\mathbf{R^7}$ and $\mathbf{R^8}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 groups independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkoxyC_{1-4}alkoxy, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

$\mathbf{R^4}$ is selected from hydrogen, halo or $-X^4R^{14}$;

X^4 is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

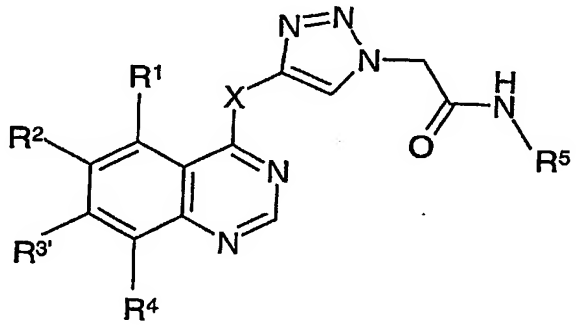
R^{14} is selected from hydrogen, $C_{1-6}alkyl$, $C_{2-6}alkenyl$ and $C_{2-6}alkynyl$;

R^5 is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $C_{1-4}alkoxy$, $CONHR^{17}$, $NHCOR^{18}$ and $S(O)_pR^{19}$ where p is 0, 1 or 2;

R^9, R^{10}, R^{15} and R^{16} are independently selected from hydrogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}cycloalkylC_{1-3}alkyl$, $hydroxyC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $aminoC_{1-6}alkyl$, $C_{1-6}alkylaminoC_{1-6}alkyl$ and $di(C_{1-6}alkyl)aminoC_{1-6}alkyl$;

R^{17}, R^{18} and R^{19} are independently selected from hydrogen, $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$, $C_{2-4}alkenyl$ and $C_{2-4}alkynyl$.

In a further aspect the present invention provides a compound of formula (IA)



formula (IA)

where X, R^1, R^2, R^4 and R^5 are as defined in relation to formula (I) and

$R^{3'}$ is hydrogen, halo or $-X^{3'}R^{13'}$;

$X^{3'}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$R^{13'}$ is a group selected from $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-6}cycloalkyl$ and $C_{3-6}cycloalkenyl$ where the group is substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, $C_{1-6}alkyl$, $phosphonoooxyC_{1-6}alkyl$, $C_{1-3}alkoxyC_{1-6}alkyl$, $phosphonoooxyC_{1-4}alkoxyC_{1-4}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}cycloalkylC_{1-3}alkyl$, $phosphonoooxyC_{3-6}cycloalkyl$, $phosphonoooxyC_{1-4}alkylC_{3-6}cycloalkyl$, $phosphonoooxyC_{3-6}cycloalkylC_{1-3}alkyl$, $C_{1-3}alkoxyC_{3-6}cycloalkyl$, $C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl$, $haloC_{1-6}alkyl$, $haloC_{3-6}cycloalkyl$, $haloC_{3-6}cycloalkylC_{1-3}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $cyanoC_{1-4}alkyl$, $aminoC_{1-6}alkyl$, $C_{1-3}alkylaminoC_{1-6}alkyl$ and $di(C_{1-3}alkyl)aminoC_{1-6}alkyl$; provided that at least one of $R^{7'}$ and $R^{8'}$ contains a phosphonooxy substituent;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is substituted on carbon or nitrogen by 1 or 2 groups independently selected from phosphonooxy, phoshonooxyC_{1-4}alkyl and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring -CH_2- is optionally replaced with a –C(O)-.

In this specification the term alkyl when used either alone or as a suffix or prefix includes straight-chain and branched-chain saturated structures comprising carbon and hydrogen atoms. References to individual alkyl groups such as propyl are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. An analogous convention applies to other generic terms such as alkenyl and alkynyl.

Cycloalkyl is a monocyclic alkyl group, and cycloalkenyl and cycloalkynyl are monocyclic alkenyl and alkynyl groups respectively.

The prefix C_{m-n} in C_{m-n}alkyl and other terms (where m and n are integers) indicates the range of carbon atoms that are present in the group, for example C_{1-3}alkyl includes C_1alkyl (methyl), C_2alkyl (ethyl) and C_3alkyl (propyl or isopropyl).

The terms C_{m-n}alkoxy comprise –O-C_{m-n}alkyl groups.

The term halo includes fluoro, chloro, bromo and iodo.

Aryl groups may be monocyclic or bicyclic.

Unless otherwise stated heteroaryl groups are monocyclic or bicyclic aromatic rings containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen or sulphur may be oxidised.

Heterocyclyl is a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring containing 4 to 7 ring atoms of which 1, 2 or 3 ring atoms selected from nitrogen, sulphur or oxygen, which may be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-; wherein a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s); wherein a ring –NH is optionally substituted by acetyl, formyl, methyl or mesyl; and wherein a ring is optionally substituted by 1 or 2 groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxy and haloC_{1-4}alkyl. When heterocyclyl is used within the definition of R^3, in one aspect of the invention it is a saturated monocyclic

ring containing 4 to 7 ring atoms of which 1 or 2 are nitrogen and where the ring is optionally substituted by C_{1-4}alkyl, hydroxyC_{1-4}alkyl and hydroxy.

Phosphonooxy is in one aspect a group of formula $-OP(O)(OH)_2$. However the term phosphonooxy also includes salts such as those formed with alkali metal ions such as sodium or potassium ions or alkaline earth metal ions, for example calcium or magnesium ions.

This specification also makes use of several composite terms to describe groups comprising more than one functionality. Such terms are to be interpreted as is understood in the art. For example C_{m-n}cycloalkylC_{m-n}alkyl comprises C_{m-n}alkyl substituted by C_{m-n}cycloalkyl.

HaloC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 halo substituents. Similarly, haloC_{m-n}cycloalkyl and haloC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 halo substituents.

HydroxyC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 hydroxy substituents. Similarly, hydroxyC_{m-n}cycloalkyl and hydroxyC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 hydroxy substituents.

C_{m-n}alkoxyC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 C_{m-n}alkoxy substituents. Similarly, C_{m-n}alkoxyC_{m-n}cycloalkyl and C_{m-n}alkoxyC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 C_{m-n}alkoxy substituents.

Where optional substituents are chosen from 1 or 2 or from 1, 2, or 3 groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups i.e. all substituents being the same or the substituents being chosen from two or more of the specified groups i.e. the substituents not being the same.

Unless specifically stated the bonding atom of a group may be any atom of that group so for example propyl includes prop-1-yl and prop-2-yl.

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 6.6 or ACD Name Batch version 6.0).

Suitable values for any R group or any part or substituent for such groups include:

for C_{1-4}alkyl:	methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl;
for C_{1-6}alkyl:	C_{1-4}alkyl, pentyl, neopentyl, dimethylbutyl and hexyl;
for C_{2-4}alkenyl:	vinyl, allyl and but-2-enyl;
for C_{2-6}alkenyl:	C_{2-4}alkenyl, 3-methylbut-2-enyl and 3-methylpent-2-enyl;
for C_{2-4}alkynyl:	ethynyl, propargyl and prop-1-ynyl;
for C_{2-6}alkynyl:	C_{2-4}alkynyl, pent-4-ynyl and 2-methylpent-4-ynyl;

for C_{3-6}cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

for C_{3-6}cycloalkenyl: cyclobutenyl, cyclopentenyl, cyclohexenyl and cyclohex-1,4-dienyl;

for C_{3-6}cycloalkylC_{1-3}alkyl: cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl and cyclobutylethyl;

for C_{1-4}alkoxy: methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy;

for C_{1-3}alkoxyC_{1-4}alkyl: methoxymethyl, methoxyethyl, methoxypropyl and ethoxyethyl;

for C_{1-3}alkoxyC_{1-6}alkyl: C_{1-3}alkoxyC_{1-4}alkyl, methoxybutyl and ethoxybutyl;

for C_{1-3}alkoxyC_{3-6}cycloalkyl: methoxycyclobutyl, methoxycyclopentyl and ethoxycyclopentyl;

for C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl: methoxycyclobutylmethyl and methoxycyclopentylmethyl;

for C_{1-4}alkoxyC_{1-4}alkoxy: methoxymethoxy, methoxyethoxy and ethoxyethoxy;

for hydroxyC_{1-4}alkyl: hydroxymethyl, 2-hydroxyethoxy and 3-hydroxypropoxy;

for hydroxyC_{1-6}alkyl: hydroxyC_{1-4}alkyl, 3-hydroxypentyl and 6-hydroxyhexyl;

for hydroxyC_{3-6}cycloalkyl: 2-hydroxycyclopropyl, 2-hydroxycyclobutyl and 2-hydroxycyclopentyl;

for hydroxyC_{3-6}cycloalkylC_{1-3}alkyl: 2-hydroxycyclopropylmethyl and 2-hydroxycyclobutylmethyl;

for hydroxyC_{1-4}alkylC_{3-6}cycloalkyl: 1-(hydroxymethyl)cyclopentyl;

for hydroxyC_{1-4}alkoxyC_{1-4}alkyl: 2-(2-hydroxyethyl)ethyl;

for haloC_{1-6}alkyl: chloromethyl, trifluoromethyl and 3,3,3-trifluoropropyl;

for haloC_{3-6}cycloalkyl: 2-chlorocyclopropyl and 2-chlorocyclobutyl;

for haloC_{3-6}cycloalkylC_{1-3}alkyl: 2-chlorocyclopropylmethyl and 2-chlorocyclobutylmethyl;

for cyanoC_{1-4}alkyl: cyanomethyl and 2-cyanoethyl;

for aminoC_{1-6}alkyl: aminomethyl, 2-aminoethyl, 2-aminopropyl and 4-aminobutyl;

for C_{1-3}alkylaminoC_{1-6}alkyl: 2-(methylamino)ethyl and 3-(ethylaminopropyl);

for di(C_{1-3}alkyl)aminoC_{1-6}alkyl: 2-(dimethylamino)ethyl 2-[methyl(ethyl)amino]ethyl and 2-(diethylamino)ethyl;

for C_{1-6}alkylamino: methylamino, ethylamino, propylamino and isopropylamino;

for di(C_{1-6}alkyl)amino: dimethylamine, methyl(ethyl)amino and diethylamino;

for aryl: phenyl and naphthyl

for heteroaryl: furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl and quinolinyl

for heterocyclyl: azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl, pyridyl, imidazolyl, tetrahydrofuranyl, tetrahydropyranyl, furanyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydro-2H-pyranyl and morpholinyl.

for phosphonooxyC_{1-6}alkyl: phosphonooxymethyl and 2-phosphonooxyethyl;

for phosphonooxyC_{3-6}cycloalkylC_{1-3}alkyl: 2-phosphonooxycyclopropylmethyl and 2-phosphonooxycyclobutylmethyl;

for phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl: 1-(phosphonooxymethyl)cyclopentyl;

for phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl: 2-(2-hydroxyethoxy)ethyl.

Within the present invention, it is to be understood that, insofar as certain of compounds of formula (I) or formula (IA) herein defined may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of formula (I) or formula (IA) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain compounds of formula (I) or formula (IA) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity.

The present invention relates to the compounds of formula (I) or formula (IA) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (I) or formula (IA) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of compounds of formula (I) or formula (IA) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to furmarate, methanesulphonate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where compounds of formula (I) or formula (IA) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine, ethanolamine, diethanolamine, triethanolamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine or amino acids such as lysine.

The compounds of formula (I) or formula (IA) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (I) or formula (II) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups

for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-C_{1-4}alkylcarbamoyl and *N*-(di-C_{1-4}alkylaminoethyl)-*N*-C_{1-4}alkylcarbamoyl (to give carbamates); di-C_{1-4}alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, C_{1-4}alkylaminomethyl and di-(C_{1-4}alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^AC(O)OC_{1-6}$alkyl-CO-, wherein R^A is for example, benzyloxy-C_{1-4}alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-C_{1-4}piperazino-C_{1-4}alkyl, piperazino-C_{1-4}alkyl and morpholino-C_{1-4}alkyl.

Preferred values of X, R^1, R^2, R^3, $R^{3'}$, R^4 and R^5 for compounds of formula (I) and formula (IA) are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the invention X is NR^6. In another aspect X is NH.

In one aspect of the invention R^6 is hydrogen or methyl. In another aspect R^6 is hydrogen.

In one aspect of the invention R^1 is hydrogen or $-OR^{11}$. In another aspect R^1 is hydrogen.

In one aspect of the invention X^1 is a direct bond or -O-. In another aspect X^1 is a direct bond.

In one aspect of the invention R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl or C_{1-4}alkyl (optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino). In another aspect R^{11} is hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy. In another aspect R^{11} is hydrogen.

In one aspect of the invention R^2 is hydrogen or $-OR^{12}$. In another aspect R^2 is hydrogen or methoxy. In a further aspect R^2 is hydrogen. In yet a further aspect R^2 is methoxy.

In one aspect of the invention X^2 is a direct bond or -O-.

In one aspect of the invention R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted by heterocyclyl) or heterocyclyl. In another aspect R^{12} is hydrogen or C_{1-4}alkyl. In another aspect of the invention R^{12} is hydrogen. In a further aspect of the invention R^{12} is methyl.

In one aspect of the invention R^3 is $-X^3R^{13}$. In a further aspect R^3 is selected from 3-chloropropoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-piperidin-1-ylpropoxy, 3-pyrrolidin-1-ylpropoxy, 3-(diethylamino)propoxy, 3-piperazin-1-ylpropoxy, 3-[(2-hydroxyethyl)(methyl)amino]propoxy, 3-(cyclopropylamino)propoxy, 3-{[2-(dimethylamino)ethyl](methyl)amino}propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-[bis(2-hydroxyethyl)amino]propoxy, 3-[ethyl(methyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-{[2-(dimethylamino)ethyl](ethyl)amino}propoxy, 3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[(cyclopropylmethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[methyl(propargyl)amino]propoxy, 3-[allyl(methyl)amino]propoxy, 3-[isobutyl(methyl)amino]propoxy, 3-(3-hydroxypiperidin-1-yl)propoxy, 3-[4-(hydroxymethyl)piperidin-1-yl]propoxy, 3-[methyl(propyl)amino]propoxy, 3-[cyclopropylmethyl(propyl)amino]propoxy, 3-{[2-(diethylamino)ethyl](methyl)amino}propoxy, 3-{[2-(diethylamino)ethyl](ethyl)amino}propoxy, 3-(4-methyl-1,4-diazepan-1-yl)propoxy, 3-[(2-hydroxyethyl)(isopropyl)amino]propoxy, 3-[cyclopropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy, 3-[cyclobutylmethyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxy)propargylamino]propoxy, 3-[allyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)neopentylamino]propoxy, 3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-azetidin-3-ylpropoxy, 3-[cyclopentyl(2-hydroxyethyl)amino]propoxy, 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy, 3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy and 3-(dimethylamino)propoxy. In another aspect R^3 is selected from 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy and 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy. In a further aspect R^3 is 3-chloropropoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy and 3-[(2-hydroxyethyl)(propyl)amino]propoxy.

In one aspect of the invention X^3 is -CH_2=CH_2-, -O- or -NH-. In another aspect X^3 is -O-.

In one aspect of the invention R^{13} is C_{1-6}alkyl substituted by $-NR^7R^8$, heterocyclyl or halo. In a further aspect of the invention R^{13} is ethyl or propyl, both of which are substituted by $-NR^7R^8$, heterocyclyl or halo. In yet a further aspect of the invention R^{13} is propyl substituted by chloro, $-NR^7R^8$ or a heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the heterocyclyl is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl. In another aspect R^{13} is propyl substituted by chloro or $-NR^7R^8$. In a further aspect R^{13} is propyl substituted by $-NR^7R^8$.

In one aspect of the invention R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl and hydroxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2$- is optionally replaced with -C(O)-. In a further aspect R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethylpropyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, propargyl, 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the ring is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl. In yet another aspect R^7 and R^8 are independently selected from hydrogen, ethyl, propyl, isobutyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethyl, 2-methoxyethyl, cyclobutyl and cyclopropylmethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl, where the ring is optionally substituted by hydroxymethyl or 2-hydroxyethyl. In a further aspect R^7 and R^8 are independentlyl propyl or 2-hydroxyethyl; or R^7 and R^8 together with the nitrogen to which they are attached form pyrrolidinyl substituted by hydroxymethyl.

In one aspect of the invention R^4 is hydrogen.

In one aspect of the invention R^5 is aryl optionally substituted by 1 or 2 halo. In another aspect R^5 is phenyl optionally substituted by 1 or 2 fluoro or chloro. In a further aspect R^5 is phenyl optionally substituted by 1 or 2 fluoro. In yet another aspect R^5 is 2,3-difluorophenyl or 3-fluorophenyl. In another aspect R^5 is 3-fluorophenyl.

In one aspect of the invention $R^{3'}$ is $-X^{3'}R^{13'}$. In a further aspect $R^{3'}$ is selected from 3-[propyl(2-phosphonooxyethyl)amino]propoxy, 3-(2-phosphonooxymethylpyrrolidin-1-yl)propoxy, 3-[ethyl(2-phosphonooxyethyl)amino]propoxy, 3-[(2-methoxyethyl)(2-phosphonooxyethyl)amino]propoxy, 3-[cyclobutyl(2-phosphonooxyethyl)amino]propoxy, 3-[4-(2-phosphonooxymethyl)piperazin-1-yl]propoxy and 3-[(1,1-dimethyl-3-phosphonooxypropyl)amino]propoxy.

In one aspect of the invention $X^{3'}$ is $-CH_2=CH_2-$, -O- or -NH-. In a further aspect $X^{3'}$ is -O-.

In one aspect of the invention $R^{13'}$ is C_{1-6}alkyl substituted by $-NR^{7'}R^{8'}$. In a further aspect of the invention $R^{13'}$ is propyl substituted by $-NR^{7'}R^{8'}$.

In one aspect of the invention $R^{7'}$ is selected from hydrogen, heterocyclyl, C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, cyanoC_{1-4}alkyl and C_{3-6}cycloalkyl. In another aspect $R^{7'}$ is ethyl, propyl, cyclobutyl or 2-methoxyethyl.

In one aspect of the invention $R^{8'}$ is phosphonooxyC_{1-4}alkyl or phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl. In another aspect $R^{8'}$ is 2-phosphonooxyethyl or 1,1-dimethyl-3-phosphonooxypropyl.

In one aspect of the invention $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl.

A preferred class of compounds is of formula (I) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen or $-OR^{11}$;

X^1 is a direct bond or -O-;

R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl, C_{1-4}alkyl optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino;

R^2 is hydrogen or $-OR^{12}$;

R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted by heterocyclyl) or heterocyclyl;

R^3 is $-X^3R^{13}$;

X^3 is $-CH_2=CH_2-$, -O- or -NH-;

R^{13} is C_{1-6}alkyl substituted by $-NR^7R^8$, heterocyclyl or halo;

R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl and hydroxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with –C(O)-;

R^4 is hydrogen; and

R^5 is aryl optionally substituted by 1 or 2 halo.

A further preferred class of compounds is of formula (I) wherein:

X is NH;

R^1 is hydrogen;

R^2 is hydrogen or methoxy;

R^3 is $-X^3R^{13}$;

X^3 is -O-;

R^{13} is propyl substituted by chloro or $-NR^7R^8$;

R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethylpropyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, propargyl, 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the ring is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl;

R^4 is hydrogen; and

R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

A further preferred class of compounds is of formula (I) wherein:

X is NH;

R^1 is hydrogen;

R^2 is hydrogen or methoxy;

R^3 is $-X^3R^{13}$;

X^3 is -O-;

R^{13} is propyl substituted by chloro or $-NR^7R^8$;

R^7 and R^8 are independently propyl or 2-hydroxyethyl; or R^7 and R^8 together with the nitrogen to which they are attached form pyrrolidinyl substituted by hydroxymethyl or 2-hydroxyethyl;

R^4 is hydrogen; and

R^5 is 3-fluorophenyl.

A preferred class of compounds is of formula (IA) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen or $-OR^{11}$;

R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl, C_{1-4}alkyl optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino;

R^2 is hydrogen or $-OR^{12}$;

R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted with heterocyclyl) or heterocyclyl;

$R^{3'}$ is $-X^{3'}R^{13'}$;

$X^{3'}$ is $-CH_2=CH_2-$, -O- or -NH-;

$R^{13'}$ is C_{1-6}alkyl substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ is selected from hydrogen, heterocyclyl, C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, cyanoC_{1-4}alkyl and C_{3-6}cycloalkyl;

$R^{8'}$ is phosphonooxyC_{1-4}alkyl or phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl;

R^4 is hydrogen; and

R^5 is aryl optionally substituted by 1 or 2 halo.

Preferred compounds of the invention are any one of:

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

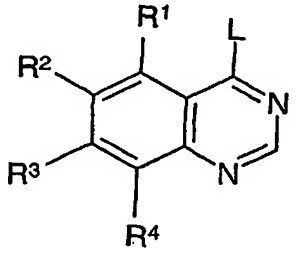
N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide; and

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide.

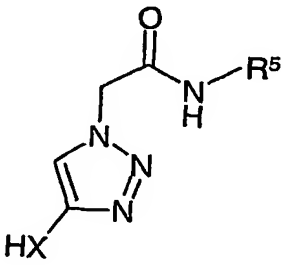
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, which process comprises reacting a compound of formula (II)



(II)

where L is a suitable leaving group such as chloro, bromo, SMe etc.

with a compound of formula (III)



(III)

in the presence of hydrochloric acid in dioxane under an inert atmosphere,

and thereafter if necessary:

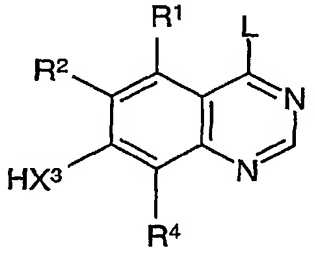
i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, ester or prodrug thereof.

The reaction is suitably effected in an organic solvent such as dimethyl acetamide or isopropanol at elevated temperatures of from 80°C to 120°C for 30 minutes to 2 hours.

The process may further comprise a process for the preparation of a compound of formula (II) when R^3 is $-X^3R^{13}$, which process comprises reacting a compound of formula (IV)



(IV)

with a compound of formula (V)

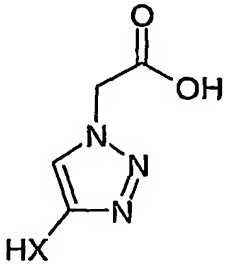
$$L^1\text{-}R^{13}$$

(V)

where L^1 is an appropriate leaving group such as chloro or L^1 is –OH which is suitably activated by a reagent such as PPh_3.

Compounds of formula (IV) and formula (V) are either known in the art or can be derived from other compounds known in the art by conventional methods which would be apparent from the literature.

The process may further comprise a process for the preparation of a compound of formula (III) which process comprises the reaction of a compound of formula (VI)



(VI)

with a compound of formula (VII)

$$R^5\text{-}NH_2$$

(VII)

The reaction is suitably effected in an organic solvent such as dimethylformamide or dimethylacetamide, with a base such as diisopropyl(ethyl)amine and with the addition of O-(7-azabenzotriazol-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate, maintaining a temperature of less than 40°C for 30 minutes to 2 hours.

Compounds of formula (VII) are known in the art or can be derived from other compounds known in the art by conventional methods which would be apparent to the skilled person from the literature.

A compound of formula (VI) when X is NR^6, can be prepared by a process that comprises the:

a) reaction of $C_{1\text{-}20}$alkyl azidoacetate with propiolic acid, followed by

b) reaction of the product of a) with a reagent such as diphenylphosphonyl azide.

The reaction in a) is suitable effected in solvents such as chloroform, dichloromethane or toluene, at a temperature of 55°C to 100°C for 30 minutes to 5 hours, and the reaction in b) is effected in dioxane, under an inert atmosphere, under reflux for 2 to 7 hours.

Further provided is a process for the preparation of a compound of formula (IA) or a pharmaceutically acceptable salt thereof, which process comprises phosphorylation of a suitable compound of formula (I) by reacting a compound of formula (I) and tetrazole with di-tert-butyl diethylphosphoramidite in an appropriate organic solvent such as dimethylformamide or dimethylacetamide under an inert atmosphere, followed by (after 1 to 5 hours) the addition of hydrogen peroxide and sodium metabisulphite. Deprotection of the phosphate group then yields a compound of formula (IA). Deprotection is suitably effected with hydrochloric acid in dioxane or dichloromethane (DCM) at ambient temperature for 6 to 30 hours.

Suitable reaction conditions are illustrated hereinafter.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation

of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

Also provided is a pharmaceutical composition which comprises a compound of formula (IA), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using

conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, for use in therapy. In addition a compound of formula (IA) or a pharmaceutically acceptable salt thereof is provided for use in therapy.

Further provided is a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, for use as a medicament and also a compound of formula (IA), or a pharmaceutically acceptable salt thereof, for use as a medicament.

Additionally a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof is provided for use in a method of treatment of a warm-blooded animal such as man by therapy. A compound of formula (IA) or a pharmaceutically acceptable salt thereof is also provided for use in a method of treatment of a warm-blooded animal such as man by therapy.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial. The use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial is also provided. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial. Preferably Aurora-B kinase is inhibited.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast or pancreatic cancer or leukaemia. Also provided is the use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast or pancreatic cancer or leukaemia.

According to yet another aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt ester or prodrug thereof for use in the method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is

beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. Further provided is a compound of formula (IA) or a pharmaceutically acceptable salt thereof for use in the method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt thereof. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial. Preferably Aurora-B kinase is inhibited.

Further provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast or pancreatic cancer or leukaemia, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. A compound of formula (IA) is also provided for use in the method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast or pancreatic cancer or leukaemia, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

For the above mentioned therapeutic uses the dose administered will vary with the compound employed, the mode of administration, the treatment desired, the disorder indicated and the age and sex of the animal or patient. The size of the dose would thus be calculated according to well known principles of medicine.

In using a compound of formula (I) or formula (IA) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.05 mg/kg to 50 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used.

The treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or

chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestratrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine-threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

In addition to their use in therapeutic medicine, a compound of formula (I) and a pharmaceutically acceptable salt, ester or prodrug thereof are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The compounds of the invention inhibit the serine-threonine kinase activity of the Aurora kinases, in particular Aurora-A kinase and/or Aurora-B kinase and thus inhibit the cell cycle and cell proliferation. Compounds which inhibit Aurora-B kinase are of particular interest. These properties may be assessed for example, using one or more of the procedures set out below.

(a) In Vitro Aurora-A kinase inhibition test

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-A may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-A, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life technologies). The 5' PCR primer contained a recognition sequence for the restriction endonuclease BamH1 5' to the Aurora-A coding sequence. This allowed the insertion of the Aurora-A gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the Aurora-A stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1. This additional coding sequence (5' TAC CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutin epitope tagged Aurora-A protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the Aurora-A gene was transformed

into E. coli DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the Aurora-A gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding Aurora-A. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL) following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant Aurora-A protein.

For the large scale expression of Aurora-A kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-A recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0 x 10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.4 at 4°C , 100 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 3 x 10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000g for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 μl Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound Aurora-A protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol).

An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active Aurora-A kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of Aurora-A enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20µl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10µl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 6.25mM ATP, 7.5µM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2µCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100µl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, the compounds of the invention generally give 50% inhibition of enzyme activity at concentrations of 1nM to 1000nM and in particular compound 1 in Table 1 gave 50% inhibition of enzyme activity at a concentration of 0.9µM and compound 3 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 0.5µM

(b) <u>In Vitro Aurora-B kinase inhibition test</u>

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-B may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-B, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the pFastBac system in a manner

similar to that described above for Aurora-A (i.e. to direct expression of a 6-histidine tagged Aurora-B protein).

For the large scale expression of Aurora-B kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-B recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0×10^8 cells were thawed and diluted with lysis buffer (50 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.5 at 4°C , 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 1 mM dithiothreitol, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 2×10^7 cells. Lysis was achieved using a sonication homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 1.0 ml CM sepharose Fast Flow (Amersham Pharmacia Biotech) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (50 mM HEPES pH7.4 at 4°C , 1 mM dithiothreitol). Bound Aurora-B B protein was eluted from the column using a gradient of elution buffer (50 mM HEPES pH7.4 at 4°C , 0.6 M NaCl, 1 mM dithiothreitol, running from 0% elution buffer to 100% elution buffer over 15 minutes at a flowrate of 0.5 ml/min). Elution fractions (1.0 ml) corresponding to the peak in UV absorbance was collected. Elution fractions were dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.05% (v/v) IGEPAL CA630 (Sigma Aldrich), 1 mM dithiothreitol). Dialysed fractions were assayed for Aurora-B kinase activity.

Each new batch of Aurora-B enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 40 with enzyme diluent & 20µl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10µl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-

HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 37.5mM ATP, 25μM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2μCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100μl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, the compounds of the invention generally give 50% inhibition of enzyme activity at concentrations of 1nM to 1000nM and in particular compound 1 in Table 1 gave 50% inhibition of enzyme activity at a concentration of 0.1μM and compound 3 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 0.1μM.

(c) <u>In Vitro cell proliferation assay</u>

This and other assays can be used to determine the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line SW620 (ATCC CCL-227). This assay determines the ability of at test compound to inhibit the incorporation of the thymidine analogue, 5'-bromo-2'-deoxy-uridine (BrdU) into cellular DNA. SW620 or other adherent cells were typically seeded at $1x10^5$ cells per well in L-15 media (GIBCO) plus 5% foetal calf serum, 1% L-glutamine (100μl / well) in 96 well tissue culture treated 96 well plates (Costar) and allowed to adhere overnight. The following day the cells were dosed with compound (diluted from 10mM stock in DMSO using L-15 (with 5% FCS, 1% L-glutamine). Untreated control wells and wells containing a compound known to give 100% inhibition of BrdU incorporation were included on each plate. After 48 hours in the presence / absence of test compound the ability of the cells to incorporate BrdU over a 2 hour labelling period was determined using a Boehringer (Roche) Cell Proliferation BrdU ELISA kit (cat. No. 1 647 229) according to manufacturers directions. Briefly, 15μl of BrdU labelling reagent (diluted 1:100 in media – L-15, 5% FCS, 1% L-glutamine) was added to each well and the plate returned to a humidified (+5% CO_2) 37°C incubator for 2 hours. After 2 hours the labelling reagent was removed by decanting and tapping the plate on a paper towel. FixDenat solution (50μl per well) was added and the plates incubated at room

temperature for 45mins with shaking. The FixDenat solution was removed by decanting and tapping the inverted plate on a paper towel. The plate was then washed once with phosphate buffered saline (PBS) and 100µl /well of Anti-BrdU-POD antibody solution (diluted 1:100 in antibody dilution buffer) added. The plate was then incubated at room temperature with shaking for 90min. Unbound Anti-BrdU-POD antibody was removed by decanting and washing the plate 4 times with PBS before being blotted dry. TMB substrate solution was added (100µl/well) and incubated for approximately 10 minutes at room temperature with shaking until a colour change was apparent. The optical density of the wells was then determined at 690nm wavelength using a Titertek Multiscan plate reader. The values from compound treated, untreated and 100% inhibition controls were used to determine the dilution range of a test compound that gave 50% inhibition of BrdU incorporation. The compounds of the invention are generally active at 1nM to 100µM in this test.

(d) In Vitro cell cycle analysis assay

This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and SW620 cells are included here as an example. SW620 cells were seeded at 7 x 10^5 cells per T25 flask (Costar) in 5 ml L-15 (5% FCS, 1% L-glutamine). Flasks were then incubated overnight in a humidified 37^{0}C incubator with 5% CO_2. The following day, 5µl of L-15 (5% FCS, 1% L-glutamine) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask. A no compound control treatment was also included (0.5% DMSO). The cells were then incubated for a defined time (24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37^{0}C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 5ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated to leave 200µl of the PBS/BSA solution. The pellet was resuspended in this 200µl of solution by pipetting 10 times to create a single cell suspension. One ml of ice-cold 80% ethanol was slowly added to each cell suspension and the samples stored at -20°C overnight or until required for staining. Cells were pelleted by centrifugation, ethanol aspirated off and pellets resuspended in 200µl PBS containing 100µg/ml RNAse (Sigma Aldrich) & 10µg/ml

Propidium Iodide (Sigma Aldrich). Cell suspensions were incubated at 37°C for 30min, a further 200µl PBS added and samples stored in the dark at 4°C overnight.

Each sample was then syringed 10 times using 21-guage needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 30,000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells with 2N (G0/G1), 2N-4N (S phase) and with 4N (G2/M) DNA content.

The compounds of the invention are generally active in this test at 1nM to 10µM.

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:
(i) evaporations were carried out by rotary evaporation *in vacuo* and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
(ii) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of an inert gas such as argon;
(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385);
(iv) yields are given for illustration only and are not necessarily the maximum attainable;
(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured in deuterated dimethyl sulphoxide (DMSO d_6) (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using one of the following four instruments

- Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz
- Bruker DPX300 spectrometer operating at a field strength of 300MHz
- JEOL EX 400 spectrometer operating at a field strength of 400 MHz
- Bruker Avance 500 spectrometer operating at a field strength of 500MHz

Peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qu, quintet; m, multiplet; br s, broad singlet;

(vi) robotic synthesis was carried out using a Zymate XP robot, with solution additions via a Zymate Master Laboratory Station and stirred via a Stem RS5000 Reacto-Station at 25°C;

(vii) work up and purification of reaction mixtures from robotic synthesis was carried out as follows: evaporations were carried out *in vacuo* using a Genevac HT 4; column chromatography was performed using either an Anachem Sympur MPLC system on silica using 27 mm diameter columns filled with Merck silica (60 μm, 25 g); the structures of the final products were confirmed by LCMS (liquid chromatography mass spectrometry) on a Waters 2890 / ZMD micromass system using the following and are quoted as retention time (RT) in minutes:

Column:	waters symmetry C18 3.5 μm 4.6x50 mm
Solvent A:	H_2O
Solvent B:	CH_3CN
Solvent C :	MeOH + 5% HCOOH
Flow rate:	2.5 ml / min
Run time:	5 minutes with a 4.5 minute gradient from 0-100% C
Wavelength:	254 nm, bandwidth 10 nm
Mass detector:	ZMD micromass
Injection volume	0.005 ml

(viii) Analytical LCMS for compounds which had not been prepared by robotic synthesis was performed on a Waters Alliance HT system using the following and are quoted as retention time (RT) in minutes:

Column:	2.0 mm x 5 cm Phenomenex Max-RP 80A
Solvent A:	Water
Solvent B:	Acetonitrile
Solvent C:	Methanol / 1% formic acid or Water / 1% formic acid
Flow rate:	1.1 ml / min
Run time:	5 minutes with a 4.5 minute gradient from 0-95% B + constant 5% solvent C
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.005 ml
Mass detector:	Micromass ZMD

(ix) Preparative high performance liquid chromatography (HPLC) was performed on either

- Waters preparative LCMS instrument, with retention time (RT) measured in minutes:

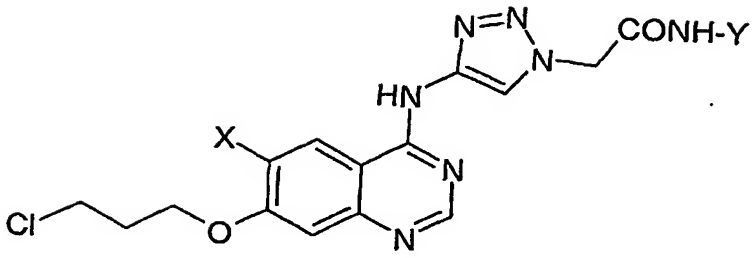
Column:	β-basic Hypercil (21x100 mm) 5μm
Solvent A:	Water / 0.1% Ammonium carbonate
Solvent B:	Acetonitrile
Flow rate:	25 ml / min
Run time:	10 minutes with a 7.5 minute gradient from 0-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	1 - 1.5 ml
Mass detector :	Micromass ZMD

- Gilson preparative HPLC instrument, with retention time (RT) measured in minutes:

Column:	21 mm x 15 cm Phenomenex Luna2 C18
Solvent A:	Water + 0.1% trifluoracetic acid,
Solvent B:	Acetonitrile + 0.1% trifluoracetic acid
Flow rate:	21 ml / min
Run time:	20 minutes with various 10 minute gradients from 5-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.1-4.0 ml

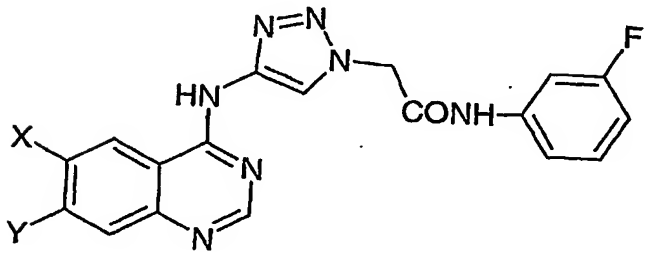
(x) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis.

Table 1



Compound	X	Y
1	OMe	3-fluorophenyl
2	H	3-fluorophenyl

Table 2



Compound	X	Y
3	OMe	**3-[(2-hydroxyethyl)(propyl)amino]propoxy**
4	OMe	**3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy**
5	H	**3-[(2-hydroxyethyl)(propyl)amino]propoxy**
6	H	**3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy**

Example 1 - Preparation of compound 1 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide

2-(4-amino-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide (400 mg, 1.7 mmol) was added to a solution of 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (488 mg, 1.7 mmol) in dimethyl acetamide (15 ml). A solution of hydrochloric acid in dioxane (4.0 N, 235 µl, 1.7 mmol) was added to the reaction mixture and the resulting solution was heated at 90 °C for 50 minutes causing a dense precipitate to form. The reaction mixture was cooled and diluted with isopropanol. The solid was recovered by suction filtration, washed with ethyl acetate and dried *in vacuo* to give compound 1 in table1 (860 mg, 85 % yield) :

^{1}H-NMR (DMSO d_6) : 9.05 (s, 1H), 8.72 (s, 1H), 8.37 (s, 1H), 7.61 (m, 1H), 7.43 (s, 1H), 7.36 (m, 2H), 6.93 (t, 1H), 5.51 (s, 2H), 4.35 (t, 2H), 4.04 (s, 3H), 3.85 (t, 2H), 2.33 (m, 2H) :

MS (+ve ESI): 486.1 $(M+H)^+$.

2-(4-amino-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide, used as starting material, was obtained as follows:

a) Ethyl azidoacetate (3.96 ml of a 3.26 N solution in dichloromethane, 10 mmol) was added to a solution of propiolic acid (700 mg, 10 mmol) in toluene (5 ml) and the reaction heated at reflux for 1 hour. The reaction was cooled and the solid was recovered, washed with diethyl ether and dried *in vacuo* to give 1-(2-ethoxy-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (1.4 g, 70 % yield) :

^{1}H-NMR (DMSO d_6) : 8.67 (s, 1H), 5.46 (s, 2H), 4.19 (q, 2H), 1.23 (t, 3H) :

MS (+ve ESI): 200.2 $(M+H)^+$.

b) Diphenylphosphoryl azide (11.7 g, 42 mmol) was slowly added to a suspension of 1-(2-ethoxy-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (7.56 g, 38 mmol) in a mixture of dry dioxane (100 ml) and 2-methylpropan-2-ol (50 ml) under argon. The solution was slowly heated to reflux and heated at reflux for 5 hours. The reaction mixture was cooled, concentrated *in vacuo*, and the residual oil diluted with a mixture of ethyl acetate (100 ml) and diethyl ether (50 ml). The solution was washed with water and brine before being concentrated *in vacuo*. Purification by chromatography on silica gel, eluting with dichloromethane : ethyl acetate (9:1 to 7:3) gave ethyl {4-[(*tert*-butoxycarbonyl)amino]-1*H*-1,2,3-triazol-1-yl}acetate as a white solid (5.52 g, 54 % yield) :

^{1}H-NMR (DMSO d_6): 10.05 (s, 1H), 7.94 (s, 1H), 5.31 (s, 2H), 4.17 (q, 2H), 1.46 (s, 9H), 1.22 (t, 3H) :

MS (+ve ESI) : 271.3 $(M+H)^+$.

c) A solution of ethyl {4-[(*tert*-butoxycarbonyl)amino]-1*H*-1,2,3-triazol-1-yl}acetate (2.7 g, 10 mmol) in ethanol (54 ml) and 2.0 N aqueous sodium hydroxide (10 ml, 20 mmol) was stirred at ambient temperature for 3 hours. The pH of the solution was then adjusted to 7, the solvent was evaporated *in vacuo*, and the pH was adjusted to 3. The precipitate was collected by suction filtartion, washed with water and dried to give {4-[(*tert*-butoxycarbonyl)amino]-1*H*-1,2,3-triazol-1-yl}acetic acid (2.35 g, 97 % yield) :

^{1}H-NMR (DMSO d_6) : 10.03 (s, 1H), 7.91 (s, 1H), 5.19 (s, 2H), 1.46 (s, 9H) :

MS (+ve ESI): 243.2 $(M+H)^+$.

d) 3-Fluoroaniline (670 mg, 6 mmol) was added to a solution of {4-[(*tert*-butoxycarbonyl)amino]-1*H*-1,2,3-triazol-1-yl}acetic acid (1.21 g, 5 mmol) in dimethyl formamide (12 ml) and diisopropylethylamine (770 mg, 6 mmol).

O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.08 g, 5.5 mmol) was added to the solution at such a rate to keep the temperature of the reaction medium below 30 °C. The mixture was stirred for 40 minutes, diluted with ethyl acetate (40 ml) and diethyl ether (40 ml) and then washed with i) sodium bicarbonate solution, ii) 0.5 N hydrochloric acid and iii) brine. The organic phase was concentrated *in vacuo* to give *tert*-butyl (1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-1,2,3-triazol-4-yl)carbamate (1.38 g, 82 % yield) :

^{1}H-NMR (DMSO d_6) : 10.65 (s, 1H), 10.04 (s, 1H), 7.95 (m, 1H), 7.55 (m, 1H), 7.38 (m, 1H), 7.30 (d, 1H), 6.93 (m, 1H), 5.28 (s, 1H), 1.46 (s, 9H) :

MS (+ve ESI): 336.2 $(M+H)^+$.

e) Trifluoroacetic acid (6 ml) was added to a suspension of *tert*-butyl (1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-1,2,3-triazol-4-yl)carbamate (1.5 g, 4.5 mmol) in dichloromethane (12 ml), and the reaction was stirred at 45 °C for 1.5 hours. The solvents were evaporated in vacuo and aqueous sodium bicarbonate solution (25 ml) was added. Extraction with ethyl acetate, followed by solvent evaporation in vacuo gave 2-(4-amino-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide as a beige solid (1.0 g, 95 % yield) :

^{1}H-NMR (DMSO d_6) : 10.60 (s, 1H), 7.55 (m, 1H), 7.37 (m, 1H), 7.3 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.13 (s, 2H), 4.73 (s, 2H) :

MS (+ve ESI): 236.2 $(M+H)^+$.

4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline, used as starting material, was obtained as follows:

f) Palladium on carbon (3.3 g of a 10 % mixture) was added to a solution of 7-(benzyloxy)-6-methoxyquinazolin-4-(3H)-one (20 g, 71 mmol) (prepared according to *J. Med. Chem.* **1999**, 42, 5369-5389) suspended in dimethylformamide (530 ml). Ammonium formate (45 g, 710 mmol) was then added portion-wise over 1.25 hour. The reaction mixture was stirred for an additional 0.5 hour and the catalyst was removed by filtration. The solvent was removed *in vacuo* to yield 7-hydroxy-6-methoxyquinazolin-4-(3H)-one (8.65 g, 64 % yield) : ^{1}H-NMR (DMSO d_6) : 7.91 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 3.90 (s, 3H).

g) A mixture of 7-hydroxy-6-methoxyquinazolin-4-(3H)-one (8.0 g, 41.6 mmol), pyridine (7.5 ml) and acetic anhydride (63 ml) was heated at 100°C for 4.5 hours and left to cool to ambient temperature for 18 hours. The reaction mixture was poured into ice/water (400 ml) and the resultant precipitate collected by filtration and dried *in vacuo*. Analysis revealed that hydrolysis of the acetate group on the 4 position of the quinazoline was incomplete. The mixture was therefore treated with water (150 ml) and pyridine (0.5 ml) at 90 °C for 15 minutes. The reaction was cooled and the solid was collected by filtration, washed with water and dried *in vacuo* to yield 7-(acetoxy)-6-methoxyquinazolin-4-(3H)-one (7.4 g, 76 % yield) : ^{1}H-NMR (DMSO d_6) : 8.05 (s, 1H), 7.65 (s, 1H), 7.45 (s, 1H), 3.90 (s, 3H), 2.31 (s, 3H).

h) Dimethylformamide (0.5 ml) was added to a solution of 7-(acetoxy)-6-methoxyquinazolin-4-(3H)-one (2.0 g, 8.5 mmol) in thionyl chloride (32 ml) and the reaction mixture was heated at reflux for 1.5 hours. Upon cooling to ambient temperature, the thionyl chloride was removed *in vacuo* and azeotroped with toluene. The residue was diluted with dichloromethane (15 ml), a solution of 10 % ammonia in methanol (80 ml) added and the mixture heated at 80°C for 10 minutes. Upon cooling to ambient temperature, the solvent was evaporated to almost complete dryness, water was added and the pH adjusted to 7 with dilute hydrochloric acid. The resultant precipitate was collected by filtration and dried *in vacuo* at 35 °C for 18 hours to yield 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g, 92 % yield) : ^{1}H-NMR (DMSO d_6) : 8.81 (s, 1H), 7.40 (s, 1H), 7.25 (s, 1H), 4.00 (s, 3H).

i) Triphenylphosphine (2.6 g, 10.1 mmol) and 3-chloropropanol (0.69 ml, 8.2 mmol) were added to a suspension of 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g, 7.8 mmol) in dichloromethane (100 ml) under argon. The flask was placed in a water bath at 20 °C and di-*tert*-butyl azodicarboxylate (2.30 g, 10.1 mmol) added portion wise over a few minutes. The reaction mixture was stirred at ambient temperature for 2 hours before solvent evaporation *in vacuo*. Purification by flash chromatography on silica gel, eluting with ethyl

acetate : petroleum ether (3:7) yielded 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (2.0 g, 91 % yield) :

^{1}H-NMR (DMSO d_6) : 8.90 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 4.42 (m, 2H), 4.05 (s, 3H), 3.80 (m, 2H), 2.31 (m, 2H).

Example 2 - Preparation of compound 2 in table 1 - 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide

2-(4-amino-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide (446 mg, 1.9 mmol) was added to a solution of 4-chloro-7-(3-chloropropoxy)quinazoline (488 mg, 1.9 mmol) in dimethylacetamide (15 ml). A solution of hydrochloric acid in dioxane (4.0 N, 475 µl, 1.9 mmol) was added to the reaction mixture and the resulting solution was heated at 90 °C for 3 hours. The mixture was cooled, diluted with isopropanol and the solid recovered by suction filtration. Washing the solid with ethyl acetate and diethyl ether, followed by prolonged drying *in vacuo*, gave compound 2 in table 1 (620 mg, 66 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 9.10 (s, 1H), 8.92 (d, 1H), 8.72 (s, 1H), 7.61 (m, 1H), 7.54 (m, 1H), 7.39 (m, 3H), 6.93 (t, 1H), 5.51 (s, 2H), 4.37 (t, 2H), 3.86 (t, 2H), 2.31 (m, 2H) :

MS (+ve ESI): 456.1 $(M+H)^+$

4-chloro-7-(3-chloropropoxy)quinazoline, used as the starting material was obtained as follows:

a) Formamidine acetate (20.13 g, 193.4 mmol) was added to a solution of 2-amino-4-fluorobenzoic acid (15.0 g, 96.7 mmol) in 2-methoxyethanol (97 ml) and the mixture heated to reflux for 18 hours. The reaction was cooled, concentrated and the residue stirred in aqueous ammonium hydroxide (0.01 N, 250 ml) for 1 hour. The suspension was filtered, washed with water and dried over phosphorus pentoxide to yield 7-fluoroquinazolin-4-ol as an off-white solid (10.35 g, 65 % yield) :

^{1}H-NMR (DMSO d_6) : 12.32 (br s, 1H), 8.19 (dd, 1H), 8.14 (s, 1H), 7.45 (m, 1H), 7.39 (m, 1H) :

^{19}F-NMR (DMSOd_6): -105 (m) :

MS (-ve ESI): 163 $(M-H)^-$,

MS (+ve ESI): 165 $(M+H)^+$.

b) Sodium hydride (14.6 g, 365 mmol) was added at 0 °C to a solution of 1,3-propanediol (27.8 g, 365 mmol) in dimethylformamide (70 ml). 7-fluoroquinazolin-4-ol (10 g, 60.9 mmol)

was added portion-wise and the reaction mixture heated at 60 °C, then at 100 °C for 3 hours. The reaction was cooled to 0 °C, quenched with water (280 ml) and adjusted to pH 5.9. The resulting suspension was filtered, washed with water then diethyl ether and dried over phosphorus pentoxide to yield 7-(3-hydroxypropoxy)quinazolin-4-ol as a white powder (12.4 g, 92 % yield) :

^{1}-HNMR (DMSO d_6) : 11.90 (br s, 1H), 8.04 (s, 1H), 8.00 (d, 1H), 7.10 (m, 2H), 4.17 (t, 2H), 3.58 (t, 2H), 1.92 (m, 2H) :

MS (+ve ESI): 221 $(M+H)^+$.

c) Dimethylformamide (1 ml) was added to a mixture of 7-(3-hydroxypropoxy)quinazolin-4-ol (10.5 g, 47.7 mmol) and thionyl chloride (100 ml, 137 mmol) and the reaction mixture heated to 85 °C for 1 hour. The mixture was cooled to ambient temperature, diluted with toluene and evaporated to dryness. This was repeated until all thionyl chloride was removed. The residue was dissolved in dichloromethane and washed with a saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organics were dried (magnesium sulphate) and concentrated to leave a yellow solid. Trituration with diethyl ether removed a less soluble impurity and the diethyl ether filtrate was concentrated to yield 4-chloro-7-(3-chloropropoxy)quinazoline as an off-white solid (8.5 g, 70 % yield) :

^{1}H-NMR (DMSO d_6) : 13.25 (br s, 1H), 8.34 (s, 1H), 8.06 (d, 1H), 7.17 (m, 2H), 4.21 (t, 2H), 3.83 (t, 2H), 2.23 (m, 2H).

MS (+ve ESI): 257, 259 $(M+H)^+$.

Example 3 - Preparation of compound 3 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide (137 mg, 0.23 mmol) was added to a solution of 2-(propylamino)ethanol (95 mg, 0.92 mmol) in dimethylacetamide (0.5 ml) in the presence of potassium iodide (76 mg, 0.46 mmol) and the reaction was heated under argon at 95 °C for 3 hours. The reaction was cooled, the solvent was evaporated *in vacuo* and the residue was purified by preparative LCMS. The fractions containing the desired compound were combined, evaporated *in vacuo* and the residue was dissolved in a mixture of dichloromethane (5 ml) and methanol (5 ml). Addition of a small volume of diethyl ether caused precipitation

of a solid which was collected by suction filtration and dried *in vacuo* to give compound 3 in table 2 (75 mg, 55 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 9.07 (s, 1H), 8.72 (s, 1H), 8.39 (s, 1H), 7.60 (d, 1H), 7.40 (m, 2H), 7.34 (d, 1H), 6.95 (t, 1H), 5.50 (s, 2H), 4.38 (m, 1H), 4.32 (m, 2H), 4.03 (s, 3H), 3.78 (m, 1H), 3.53 (m, 1H), 3.37 (m, 2H), 3.28 (m, 1H), 3.18 (m, 2H), 2.29 (m, 2H), 1.72 (m, 2H), 0.95 (m, 3H) :

MS (+ve ESI): 553.3 $(M+H)^+$.

Example 4 - Preparation of compound 4 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide

An analogous reaction to that described in example 3, but starting with (2S)-pyrrolidin-2-ylmethanol (93 mg, 0.98 mmol), yielded compound 4 in table 2 (90 mg, 66 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 9.07 (s, 1H), 8.73 (s, 1H), 8.39 (s, 1H), 7.60 (m, 1H), 7.40 (m, 2H), 7.34 (m, 1H), 6.94 (m, 1H), 5.51 (s, 1H), 4.33 (m, 2H), 4.03 (s, 3H), 3.77 (m, 1H), 3.59 (m, 4H), 3.25 (m, 2H), 2.31 (m, 2H), 2.13 (m, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.79 (m, 1H) :

MS (+ve ESI) : 551.3 $(M+H)^+$.

Example 5 - Preparation of compound 5 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-1,2,3-triazol-1-yl)-*N*-(3-fluorophenyl)acetamide (138 mg, 2.8 mmol) was added to a solution of 2-(propylamino)ethanol (115 mg, 11.2 mmol) in dimethylacetamide (0.5 ml) in the presence of potassium iodide (93 mg, 5.6 mmol) and the reaction heated under argon at 90 °C for 3 hours. The reaction was cooled, the solvent was evaporated *in vacuo* and the residue was purified by preparative LCMS. The fractions containing the desired compound were combined, evaporated *in vacuo* and the residue was dissolved in a mixture of dichloromethane (5 ml) and methanol (5 ml). Addition of a small volume of diethyl ether caused precipitation of a solid which was collected by suction filtration and dried *in vacuo* to give compound 5 in table 2 (85 mg, 58 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 9.11 (s, 1H), 8.92 (d, 1H), 8.72 (s, 1H), 7.60 (d, 1H), 7.53 (m, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 6.94 (t, 1H), 5.51 (s, 2H), 4.33 (t, 2H), 3.79 (t, 2H), 3.35 (m, 2H), 3.27 (m, 2H), 3.15 (m, 2H), 2.26 (m, 2H), 1.73 (m, 2H), 0.95 (m, 3H) :

MS (+ve ESI): 523.0 $(M+H)^+$.

Example 6 - Preparation of compound 6 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-1,2,3-triazol-1-yl}acetamide

An analogous reaction to that described in example 5, but starting with (2S)-pyrrolidin-2-ylmethanol (105 mg, 1.12 mmol), yielded compound 6 in table 2 (60 mg, 41 % yield) :

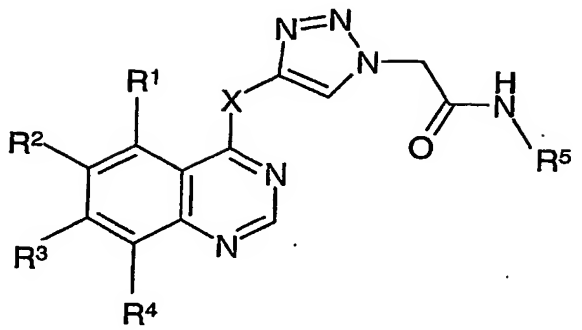
^{1}H-NMR (DMSO d_6, TFA) : 9.10 (s, 1H), 8.91 (d, 1H), 8.71 (s, 1H), 7.60 (d, 1H), 7.53 (m, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 6.94 (t, 1H), 5.51 (s, 2H), 4.33 (t, 2H), 3.78 (m, 1H), 3.63 (m, 4H), 3.27 (m, 1H), 3.19 (m, 1H), 2.27 (m, 2H), 2.14 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.80 (m, 1H) :

MS (+ve ESI): 521.0 $(M+H)^+$.

CLAIMS

What we claim is:

1. A compound of formula (I)



formula (I)

or a salt, ester or prodrug thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{11}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by heterocyclyl, halo, hydroxy C_{1-4}alkoxy or $-NR^9R^{10}$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{12}}$ is hydrogen, heterocyclyl or a group selected from aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by aryl, heterocyclyl, halo, hydroxy or $-NR^{15}R^{16}$;

$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{13}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by $-NR^7R^8$, heterocyclyl, halo, hydroxy or C_{1-4}alkoxy;

R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl;

or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 groups independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkoxyC_{1-4}alkoxy, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

R^4 is selected from hydrogen, halo or $-X^4R^{14}$;

X^4 is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

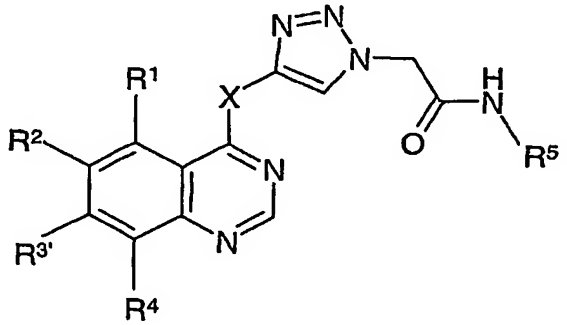
R^{14} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl;

R^5 is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, $CONHR^{17}$, $NHCOR^{18}$ and $S(O)_pR^{19}$ where p is 0, 1 or 2;

R^9, R^{10}, R^{15} and R^{16} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl and di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^{17}, R^{18} and R^{19} are independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkenyl and C_{2-4}alkynyl.

2. A compound of formula (IA)



formula (IA)

where X, R^1, R^2, R^4 and R^5 are as defined in relation to formula (I) in claim 1 and

$R^{3'}$ is hydrogen, halo or $-X^{3'}R^{13'}$;

$X^{3'}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$R^{13'}$ is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, phosphonooxyC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; provided that at least one of $R^{7'}$ and $R^{8'}$ contains a phosphonooxy substituent;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is substituted on carbon or nitrogen by 1 or 2 groups independently selected from phosphonooxy, phoshonooxyC_{1-4}alkyl and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with a –C(O)-.

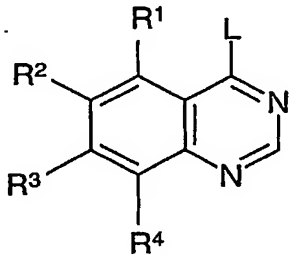
3. A compound according to claim 1 or claim 2 for use as a medicament.

4. The use of a compound according to claim 1 or claim 2, in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial.

5. The use according to claim 4 where one or more Aurora kinase(s) are Aurora-A kinase and/or Aurora-B kinase.

6. A pharmaceutical composition comprising a compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt, ester or prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

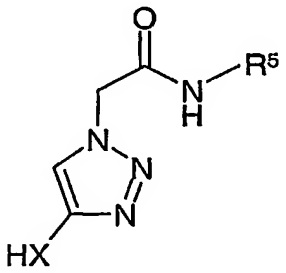
7. A process for the preparation of a compound according to claim 1 or a pharmaceutically acceptable salt, ester or prodrug thereof, which process comprises reacting a compound of formula (II)



(II)

where L is a suitable leaving group such as chloro, bromo, SMe

with a compound of formula (III)



(III)

in the presence of hydrochloric acid in dioxane under an inert atmosphere,

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

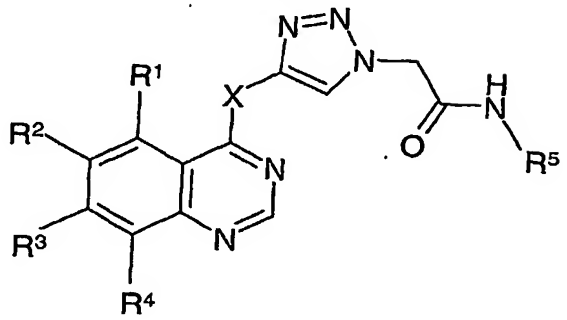
iii) forming a pharmaceutically acceptable salt, ester or prodrug thereof.

8. A process for the preparation of a compound according to claim 2 or a pharmaceutically acceptable salt thereof, which process comprises phosphorylation of a compound according to claim 1, followed by deprotection of the phosphate group to yield a compound according to claim 2.

ABSTRACT

TITLE: **CHEMICAL COMPOUNDS**

Quinazoline derivatives of formula (I)



formula (I)

for use in the treatment of proliferative diseases such as cancer and in the preparation of medicaments for use in the treatment of proliferative diseases, and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.